REMARKS/ARGUMENTS

Claims 57-84 were pending in the instant application.

Claims 62 and 73-79 were withdrawn from consideration as being drawn to a non-elected invention.

Accordingly, claims 57-61, 63-72, and 80-84 were pending and under examination in the instant application.

Claims 85-87 have been newly added. Support for these new claims can be found throughout the application as filed, *e.g.*, paragraph bridging pages 18-19, and Examples 1, 2, and 6 of the application as filed. Thus, no new matter has been added by way of the instant amendments to the claims.

Upon entry of the instant amendment, claims 57-61, 63-72, and 80-87, will be pending and under examination in this application.

Rejections Under 35 U.S.C. § 103(a):

(a) Claims 57-61, 64-72, and 80-84 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Trese *et al.* (U.S. Patent No. 5,304,118) in view of Collen *et al.* (WO 2002/50290) in further view of Wu *et al.* (U.S. Patent No. 4,774,087) (*see,* Office Action, page 3).

The Office Action relies on Trese for allegedly teaching a method of inducing posterior vitreous detachment in a human eye and treating certain diseases and dysfunctions in the eye by injecting one to three units of plasmin before or simultaneously with surgical vitrectomy (*see,* Office Action, page 4). The Office Action relies on Collen for teaching recombinant mammalian plasminogen derivatives and stabilization of such recombinant proteins (*see,* Office Action, page 4). Finally, the Office Action relies on Wu to purportedly provide motivation to use microplasmin (*see,* Office Action, page 5).

To establish a *prima facie* case of obviousness under 35 U.S.C. § 103(a), the Examiner must: (i) show that the combination of references discloses all the elements of the claim; (ii) advance "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the new invention does . . . " *KSR International Co. v. Teleflex,*

Inc., 127 S. Ct. 1727, 1731 (2007); and (iii) show a reasonable likelihood of success. The reason advanced in the Office Action to combine the cited references to arrive at Applicants' claimed invention is that allegedly "both plasmin and microplasmin share the same enzymatic activity as well known in the art, thus these are considered as art-recognized equivalents" (*see*, Office Action, page 4).

Applicants respectfully aver, for the reasons outlined below, that the reason provided in the Office Action is based on an incorrect premise that plasmin and microplasmin (1) share the same enzymatic activity; and (2) were considered "art-recognized equivalents."

First, the Declaration of Dr. Steve Pakola ("Pakola Declaration") which is attached with this Response as **Appendix A**, provides more than sufficient evidence that microplasmin and plasmin (1) do not share the same enzymatic activity; and (2) are not equivalent. The Declaration provides data comparing the properties of microplasmin and natural plasmin towards the inhibitor α2-antiplasmin and the substrates fibrin, fibrinogen, collagen type IV, gelatin, laminin, and fibronectin. More specifically, the Declaration provides data from experiments studying the kinetics of inhibition of α2-antiplasmin by plasmin and microplasmin; a comparison of plasmin and microplasmin with respect to the efficiency of fibrinolysis; and a comparison of plasmin and microplasmin with respect to hydrolysis of substrates. *See*, Pakola Declaration ¶¶ 5-12. The data from these experiments shows that microplasmin and plasmin have significantly different proteolytic activity profiles.

Second, Applicants note that the work of others have also independently supported the findings described above. Applicants draw the Examiner's attention to International Appl. No. PCT/US2005/013562 (International Publ. No. WO 2005/105990) (*see*, **Appendix B,** "Enzymatic Properties of Delta-Plasmin," pages 28-29; *see also*, U.S. Provisional Appl. No. 60/564,472, pages 27-29). These data further support the fact that microplasmin and plasmin do not share the same enzymatic activity and are not equivalent.

Third, Applicants note that kringle domains have been implicated in substrate recognition in the microplasmin molecule. In addition to the references provided with the last

Response, Applicants note that International Appl. No. PCT/US2005/013562 states in relevant part:

> The amino-terminal heavy chain of plasmin (residues 1-561, ~60 kDa) is composed of five kringle domains, each containing approximately 80 amino acid residues. The kringle domains are responsible for the regulatory properties of plasminogen, such as interaction with activation inhibitors, *e.g.*, Cl^{-1} ions; with activation stimulators, *e.g.*, ε-aminocaproic acid; with mammalian and bacterial cells; and with other proteins, such as plasmin physiological substrate fibrin and plasmin inhibitor α2-antiplasmin. (emphasis added). (*see*, **Appendix B**, page 1, lines 10-16).

Given the art-recognized importance of kringle domains described above, the absence of the kringle domains in microplasmin, would be considered by one of ordinary skill in the art to create a molecule that is significantly different in its regulatory properties from plasmin. In fact, it would teach away from and makes the utility of microplasmin for the instantly claimed purposes, unexpected. The Office Action counters that Wu *et al.* teach that microplasmin demonstrated fibrinolytic activity at about the same level on a molar basis as native plasmin. This conclusion is not supported by Wu. Indeed, no comparison was made between the proteolytic activities of "microplasmin" of Wu and plasmin using fibrin as substrate. Moreover, the proteolytic activities of "microplasmin" and plasmin using the macromolecular casein as substrate are not "at about the same level" (*see*, Example III, col. 12). As is clear from the attached Declaration of Dr. Pakola (**Appendix A**), comparative results obtained using one individual substrate cannot automatically be generalized to other individual substrates. *See*, Pakola Declaration ¶ 9. Hence, generalizing the data obtained with casein to fibrin without an actual comparative demonstration is not proper. In addition, Wu's studies are based on *in vitro* studies. The *in vitro* testing clearly is not comparable and not even close to the *in vivo* setting in the eye where the substrates form complex interconnected structures when mixed with further macromolecules. Thus, it becomes wholly unpredictable and impossible to extrapolate from Wu's *in vitro* studies to the efficacy and safety of microplasmin in pharmacological vitreolysis.

Taken together, these findings suggest, contrary to the Office Action's position, that the art did not recognize microplasmin to share the same enzymatic activity as plasmin, or to be "an art-recognized equivalent" to plasmin, and certainly not in the field of pharmacological vitreolysis. Moreover, microplasmin and plasmin do not share the same enzymatic activity.

Applicants also note that there were several additional reasons why the skilled artisan aware of the cited Trese patent disclosure would not have modified that reference to substitute microplasmin for plasmin.

First, as microplasmin is expected to diffuse better through the vitreous than plasmin, the skilled artisan would be concerned about the safety of microplasmin. Indeed, one of skill in the art would expect microplasmin not only to diffuse better through the vitreous, but also to diffuse more easily and deeper into eye tissues such as the ILM (inner limiting membrane) and/or retina. Such an effect could cause severe tissue damage, an effect certainly not desired in the eye as it would severely compromise vision. *See*, Pakola Declaration ¶ 16. Thus, one of ordinary skill would be wary of, and unlikely to consider, substituting plasmin with microplasmin for introduction into the eye.

Second, the fact that compared to natural plasmin, microplasmin is less rapidly inactivated by the inhibitor α2-antiplasmin than plasmin (*see*, Pakola Declaration ¶ 7) would further concern one of ordinary skill in the art with respect to the safety of microplasmin. For example, International Appl. No. PCT/US2005/013562, in describing the advantages of having a kringle domain having the anti-plasmin binding site in delta-plasmin (a recombinant molecule that contains kringle 1 of plasmin attached to the C-terminal serine protease domain of plasmin), states in relevant part:

> . . . presence of the α2-antiplasmin-binding sites on the domain homologous to kringle 1 can allow delta-plasmin to be inhibited rapidly by this physiological inhibitor of plasmin (a feature which can prevent bleeding); . . . (emphasis added). (*see*, **Appendix B**, page 6, lines 16-19).

Thus, one of ordinary skill in the art would be unlikely to consider moving away from a molecule with kringles to one lacking kringles that would either not be, or be less effectively, inhibited by α2-antiplasmin.

Third, one of ordinary skill in the art would expect decreased potency of microplasmin compared with plasmin and therefore assume that if microplasmin were to be used high doses would be required. High doses again raise the issue of safety concerns *in vivo*. Thus, again, one of skill would not consider replacing plasmin with microplasmin.

Taken together, these findings suggest that substitution of plasmin for microplasmin for the purpose of pharmacological vitreolysis is not one that a skilled person would consider favorably in view of the many issues arising from the molecular and enzymatic differences between the two enzymes and the potential safety concerns. One skilled in the art would not have been motivated to make the substitution nor would there have been a reasonable likelihood of success. Applicants have surprisingly found that despite these legitimate concerns of the ordinarily skilled artisan, in the claimed methods, microplasmin is both effective and safe in the eye and can be used at doses similar to plasmin.

The Office Action's reliance on MPEP § 2144.07 and *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327 (1945), is misplaced. In *Sinclair & Carroll Co.*, the inventor merely used a Carbide & Carbon catalog to choose a solvent having the peculiar qualities described by a prior art reference (the Hanson article) as being useful for the use sought by the inventor. In this case, unlike *Sinclair & Carroll Co.*, no patent, application, reference, or catalog suggested the use of microplasmin in the eye and furthermore, microplasmin was not considered an art recognized equivalent for the reasons articulated above. The two references cited by the Examiner in no way teach the equivalency of microplasmin and plasmin, and more importantly, do not teach the use of microplasmin in the eye as taught by Applicants. It is important also to note that unlike the chemical compounds of *Sinclair & Carroll Co.*, there is a great deal of unpredictability associated with modifying a known biological molecule such as an enzyme (*e.g.*, plasmin, microplasmin). The unpredictability relates not only to the enzymatic and molecular functions of the molecule, but also to its safety profile in the subject in which it is to be used. There is also great unpredictability in moving from treatment of one disease to a different indication as different mechanisms of action may also be involved. Such unpredictability would not have been of concern in *Sinclair & Carroll Co.* Furthermore, for the reasons described above, one skilled in the art would recognize reasons why microplasmin would not be expected to be safe and effective when used in the eye.

Applicants further note that combining Trese with Collen and Wu is based on nothing more than improper hindsight reasoning. As noted before, Collen and Wu do not teach or

suggest the use of microplasmin in pharmacological vitreolysis. The focus of both Collen and Wu is potential treatment of strokes through fibrinolysis. The Office Action states that the replacement of plasmin of Trese with the microplasmin of Collen and/or Wu is not because of the teaching of Collen and Wu that microplasmin is being used in treatment of strokes, but rather because one of ordinary skill would recognize microplasmin as an art-recognized equivalent to plasmin of Trese. This combination does not show microplasmin and plasmin are art-recognized equivalents as Collen and Wu are unrelated to pharmacological vitreolysis and Trese is unrelated to treatment of strokes. As noted above, microplasmin is not an art-recognized equivalent of plasmin. Nor do Collen or Wu suggest that they are equivalent. Thus that basis for the combination of the references is not proper.

It bears noting again that simply because microplasmin has been evaluated for potential treatment of strokes does not in any way make its use in treating disorders of the eye obvious. The non-obviousness of using microplasmin in eye disorders is supported by the fact that Trese, the inventor of the Examiner cited primary reference, 5,304,118 U.S. patent, followed his 5,304,118 patent with four other related patents (*see*, U.S. Patent Nos. 6,183,692; 6,207,066; 6,787,135; and 6.855,263) and five related applications (*see*, U.S. Patent Publ. Nos. 20020139378; 20030147877; 20030175263; 20040024344; and 20060024349), and despite the availability of Colleen and Wu, did not even hint or suggest the use of microplasmin as a replacement for plasmin in any of these subsequent patents or applications. Furthermore, we are not aware of any journal article publications by Trese relating to the use of plasmin-like molecules in the eye, except for one article in October 2007, well after the filing date of the instant application, that suggests the use of microplasmin as claimed herein[1]. The fact that Trese, the pioneer in this field, did not himself teach the use of microplasmin in the eye until well after the filing date of the instant application supports the non-obviousness of the claimed invention.

In summary, the Office Action has not made a *prima facie* case of obviousness because:

(i) there is no reason to combine the cited references. There are no finite number of identified, predictable solutions in this case. The plasmin sequence is 791 amino acids long.

[1] We conducted a search of the PubMed database of NCBI using the keywords "Trese" and "microplasmin."

One of ordinary skill could vary the molecule in any number of ways (*e.g.*, one could shorten the plasmin amino acid sequence in any number of ways by removing internal sequences or any number or combination of protein domains; one could alter the protein's primary sequence; or one could actually make the sequence longer). How changes in the sequence affect activity is unpredictable. In addition, as stated in the Pakola Declaration, there are numerous reasons why one of skill in the art would not combine the cited references (*see*, Pakola Declaration ¶ 16); and

(ii) the difference in activities between the two enzymes, the lack of binding domains (kringles) in microplasmin, and the potential safety concerns in moving from plasmin to microplasmin, do not in any way guarantee *a priori* a reasonable expectation of success for microplasmin to be both efficient and safe in the setting of pharmacological Vitreolysis (*see*, Pakola Declaration ¶¶ 5-13 & 16).

Thus, one of ordinary skill in the art would not have seen a benefit to modifying the prior art in the manner claimed by Applicants, and there would have been no motivation to do so.

For the foregoing reasons, Applicants respectfully request that this rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

(b) Claims 57, 63, 66, and 70 remain rejected under 35 U.S.C. § 103(a) as purportedly being unpatentable over Trese *et al.* (U.S. Patent No. 5,304,118) in view of Collen *et al.* (WO 2002/50290) in further view of Wu *et al.* (U.S. Patent No. 4,774,087) and Tanaka *et al.* (*see*, Office action, page 6).

For the reasons discussed above, the combination of Trese, Collen and Wu do not render obvious Applicants' claimed invention. Nor would there have been any reason to combine the references as proposed, as also set forth above. Tanaka does not remedy this deficiency. In fact, Tanaka further bolsters the non-obviousness of using microplasmin. Tanaka's article, published in 2000, describes, in part, enzymes useful for enzyme-assisted vitrectomy. Although Tanaka's article was published well after the description of microplasmin in the cited Wu and Collen references, Tanaka does not suggest, or even hint at, using microplasmin as an alternative to

plasmin in pharmacological vitrectomy. This further evidences the non-obviousness of using microplasmin as claimed by Applicants.

Accordingly, Applicants respectfully request that this rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

CONCLUSION

Upon entry of the instant Amendment, claims 57-61, 63-72, and 80-87 will be pending in the instant application. As set forth above, these claims are believed to be in condition for allowance. Further and favorable action in the form of a Notice of Allowance is respectfully requested.

Applicants petition for a one-month extension of time to respond to the outstanding Office Action. Please charge the fees associated with the one-month extension and the fees associated with the filing of the Request for Continued Examination to Deposit Account No. 08-0219. No additional fees are believed to be due in connection with this filing; however, if any additional fees are due, please charge the requisite fees to Deposit Account No. 08-0219.

If the Examiner has any questions relating to this application, he is encouraged to call the undersigned at the telephone number indicated below.

Respectfully submitted,

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APPENDIX A

Attached is a copy of a Declaration of Dr. Steve Pakola Under 37 C.F.R. § 1.132.